



APPENDIX A

Product Formulations Containing Multiple Active Ingredients

The Agency does not routinely include, in its risk assessments, an evaluation of mixtures of active ingredients, either those mixtures of multiple active ingredients in product formulations or those in the applicator's tank. In the case of the product formulations of active ingredients (that is, a registered product containing more than one active ingredient), each active ingredient is subject to an individual risk assessment for regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively^{1 2}.

Acute oral toxicity data (i.e., LD50 values) from mammalian studies for formulated products that contain esfenvalerate and one or more additional active ingredients are summarized below.

Currently, the Agency's guidance for assessing the potential risk of chemical mixtures is limited to human health applications (USEPA, 2000). However, the guidance includes principles for evaluating mixtures to assess potential interactive effects that are generally applicable. Consistent with EPA's Overview Document (USEPA 2004), the Agency's mixture guidance (USEPA 2000) discusses limitations in quantifying the risk of specified mixtures when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD50 values are potentially useful only to the extent that a wild mammal would consume plants or animals immediately after these dietary items were directly sprayed by the product. Increasing time post application, the differential rates of degradation, transport, etc. for the active ingredients in the formulation only permit a qualitative discussion of potential acute risk (USEPA 2004).

As discussed in USEPA (2000) a quantitative component-based evaluation of mixture toxicity requires data of appropriate quality for each component of a mixture. In this mixture evaluation LD50s, with associated 95% confidence intervals, are needed for the formulated product. The same quality of data is also required for each component of the mixture. Given that many of the formulated products do not have LD50 values of the required quality and since LD50 values are not available for all the components of these formulations a quantitative analysis of potential interactive effects is not possible.

While a quantitative evaluation of the data is not possible with currently accepted scientific methods, as a screening tool, a qualitative analysis can be used to indicate if formulated products exhibit interactive effects (e.g., synergism or antagonism).

¹ Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, Environmental Protection Agency (January 2004) (Overview Document).

² Memorandum to Office of Prevention, Pesticides and Toxic Substance, US EPA conveying an evaluation by the U.S. Fish and Wildlife Service and National Marine Fisheries Service of an approach to assessing the ecological risks of pesticide products (January 2004).

In the case of esfenvalerate, a qualitative examination of the trends in LD50 values, with the associated confidence intervals, across the range of percent active ingredient, show no discernable trends in potency that would suggest synergistic (i.e., more than additive) or antagonistic (i.e., less than additive) interactions.

To confirm a lack of interactive effects, the LD50s for the formulated products were estimated by considering the proportion and potency of each active ingredient in the mixture using the formula presented below, where r equals the relative proportion of each active ingredient (ai) in the formulated product (f)³

$$\text{Estimated LD50}_{(f)} = [r_{ai1}/\text{LD50}_{(ai1)} + r_{ai2}/\text{LD50}_{(ai2)}]^{-1}$$

The estimated LD50 formula assumes no synergistic or antagonistic interactions. Estimated LD50 values above or below the LD50 confidence intervals for the formulated product could suggest an interactive effect. In all cases where product LD50 values with associated confidence intervals were available, the estimated LD50s fell either within or near (within 2-fold the LD50) the confidence intervals for the formulated products. Given the overall variability of the available acute toxicity data, the few values that fell near, but outside the confidence intervals are not considered toxicologically significant. These results provide additional confidence that synergistic interactions are unlikely for the formulated products examined.

Based on these evaluations of the best available data and the Agency's existing guidance it is reasonable to conclude that these formulations are reflecting an independent additive toxicity response and not an interactive effect. Given that the active and inert ingredients would not be expected to have similar mechanisms of action, metabolites or toxicokinetic behavior it is also reasonable to conclude that an assumption of dose-addition would be inappropriate. Consequently, an assessment of esfenvalerate's potential effect on the CRLF when it is co-formulated with other active ingredients can be based on the toxicity of esfenvalerate.

³ Methods described in Tabashnik, BE, Evaluation of Synergism among *Bacillus thuringiensis* Toxins, Appl Environ Microbiol. 1992 Oct;58(10):3343-6.

Pesticide Products Formulated with Esfenvalerate and Other Pesticide Active Ingredients

ESFENVALERATE PRODUCTS ^{4 5}

PRODUCT/TRADE NAME	EPA Reg.No.	% Esfenvalerate	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT		PM
			LD 50 (mg/kg)	CI (mg/kg)	A.I Adjusted CI (mg/kg)	A.I Adjusted LD50 (mg/kg)	
HI-POWER INDOOR INSECT FOGGER FORMULA V	00023902624	0.1	No Data	No Data	No Data	No Data	
ORTHO ROACH, ANT AND SPIDER KILLER	00023902679	0.05	1700 ⁶	1330-2180	No Data	No Data	
SPRAYPAK ANT & ROACH KILLER FORMULA 2	00049800167	0.05	3660 ⁷	2410-5550	No Data	No Data	
SPRAYPAK INSTUTIONAL ANT AND ROACH RESIDUAL SPRAY	00049800177	0.05	>5000	NA Limit Dose	No Data	No Data	
TAT ROACH & ANT SPRAY WITH RESIDUAL ACTION 2491	00050600176	0.05	3660 ⁷	2410-5550	No Data	No Data	
TAT TOTAL RELEASE WATER BASED FOGGER	00050600181	0.1	No Data	No Data	No Data	No Data	
MULTI-USE INSECTICIDE FOGGER	00070600105	0.1	>5000	NA Limit Dose	No Data	No Data	

⁴ From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division.

⁵ Esfenvalerate: rat oral LD50= 87.2 mg/kg

⁶ Cited data based on LD50 values for a more concentrated product formula (Reg. 00102101692).

⁷ Cited data based on LD50 values for a more concentrated product formula (Reg. 00102101575).

R&M FLEA & TICK FOGGER #1	00076900584	0.1	No Data	No Data	No Data	No Data	
EVERCIDE INTERMEDIATE 2491	00102101575	2.5	3660	2410-5550	91.5	60-139	
EVERCIDE RESIDUAL PRESSURIZED SPRAY 2523	00102101594	0.05	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE RESIDUAL ANT & ROACH SPRAY 2543	00102101601	0.05	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE WASP AND HORNET SPRAY 2577	00102101613	0.031	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE CONCENTRATE 2601	00102101634	3.85	1310	1010-1700	50.4	38.9-65.5	
EVERCIDE TOTAL RELEASE FOGGER 2602	00102101635	0.1	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE CONCENTRATE 2603	00102101647	2.78	1420	1000-2030	39.5	27.8-56.4	
EVERCIDE INTERMEDIATE 2666	00102101652	1.57	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE NYLAR TOTAL RELEASE AEROSOL 2644	00102101656	0.1	>5000	NA Limit Dose	No Data	No Data	
NYLAR TOTAL RELEASE AEROSOL 2614	00102101674	0.1	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE NYLAR TOTAL RELEASE AEROSOL 2615	00102101676	0.1	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE CONCENTRATE 2595	00102101690	2.5	>2510	NA Limit Dose	No Data	No Data	
EVERCIDE CRAWLING INSECT KILLER 2548	00102101691	0.05	1700 ⁶	1330-2180	No Data	No Data	
EVERCIDE CONCENTRATE 2547	00102101692	2	1700	1330-2180	34	26.6-43.6	

EVERCIDE ROACH & ANT SPRAY 2622	00102101697	0.05	1950 ⁸	1250-3040	No Data	No Data	
EVERCIDE INTERMEDIATE 2769	00102101754	2.5	903	No C.I. Values	No Data	No Data	
EVERCIDE RESIDUAL ROACH AND ANT SPRAY 27693	00102101755	0.05	903	No C.I. Values	No Data	No Data	
EVERCIDE RESIDUAL ROACH AND ANT SPRAY 27692	00102101756	0.075	903	No C.I. Values	No Data	No Data	
EVERCIDE RESIDUAL ROACH AND ANT SPRAY 27691	00102101757	0.1	903	No C.I. Values	No Data	No Data	
EVERCIDE RESIDUAL ROACH & ANT SPRAY 27891	00102101762	0.05	903	No C.I. Values	No Data	No Data	
EVERCIDE INTERMEDIATE 2789	00102101763	1.25	903	No C.I. Values	No Data	No Data	
EVERCIDE WASP & HORNET SPRAY 26011	00102101764	0.1	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE O.B. RTU 28101	00102101787	0.05	>5000	NA Limit Dose	No Data	No Data	
EVERCIDE CONCENTRATE 2810	00102101788	2.5	>2510	NA Limit Dose	No Data	No Data	
PYROCIDAL FALCON 7452	00102101810	0.2	>2000	NA Limit Dose	No Data	No Data	
EVERCIDE EMULSIFIABLE CONCENTRATE 2845 MUP	00102101826	0.425	3129	1750-5000	13	7-21	

⁸ Cited data based on LD50 values for a more concentrated product formula (Reg. 00102101627).

EVERCIDE HOME DEFENSE 28452	00102101827	0.025	3129 ⁹	1750-5000	No Data	No Data	
SPEER RESIDUAL PRESSURIZED SPRAY	00272400583	0.05	3660 ⁷	2410-5550	No Data	No Data	
SPI TOTAL RELEASE AEROSOL FOGGER II	00272400584	0.05	No Data	No Data	No Data	No Data	
SPEER-IT FOGGER II TOTAL RELEASE AEROSOL	00272400647	0.1	>5000	NA Limit Dose	No Data	No Data	
SPEER TOTAL RELEASE AEROSOL II WITH NYLAR	00272400662	0.1	>5000	NA Limit Dose	No Data	No Data	
SPEER TOTAL RELEASE AEROSOL III WITH NLAR	00272400664	0.1	>5000	NA Limit Dose	No Data	No Data	
SPEER ANT AND ROACH KILLER II	00272400673	0.05	>5000	NA Limit Dose	No Data	No Data	
SPEER-IT FOGGER IV TOTAL RELEASE AEROSOL	00272400676	0.1	No Data	No Data	No Data	No Data	
BLACK JACK ROACH & ANT KILLER VI	00884800086	0.05	>5000	NA Limit Dose	No Data	No Data	
CB-305 FOGGER	00944400143	0.05	No Data	No Data	No Data	No Data	
CB-405 FOGGER	00944400144	0.1	No Data	No Data	No Data	No Data	
CB FOGGER IV	00944400145	0.1	No Data	No Data	No Data	No Data	
CB-405 FOGGER WB	00944400166	0.1	>5000	NA Limit Dose	No Data	No Data	
MISTY FIRE ANT INJECTOR SPRAY II	01080700191	0.1	No Data	No Data	No Data	No Data	

⁹ Cited data based on LD50 values for a more concentrated product formula (Reg. 00102101826).

UNICORN HOUSE AND CARPET SPRAY #5	02829300192	0.05	3660 ⁷	2410-5550	No Data	No Data	
UNICORN HOUSE AND CARPET SPRAY #6	02829300196	0.05	3660 ⁷	2410-5550	No Data	No Data	
ENFORCER TWO-HOUR FOGGER	04084900063	0.1	>5000	NA Limit Dose	No Data	No Data	
CS 101 ROACH & ANT SPRAY	04444600065	0.05	>5000	NA Limit Dose	No Data	No Data	
CTX/CYBER BLAST	04538500093	0.05	>5000	NA Limit Dose	No Data	No Data	
BENGAL ROACH & ANT SPRAY IV	06854300017	0.05	1700 ⁶	1330-2180	No Data	No Data	